

CORSO INTEGRATO DI GENETICA

AA 2011/12

Prof Alberto Turco

2.11.11

Lezioni 23 e 24

GENETICA CLINICA
DISMORFOLOGIA

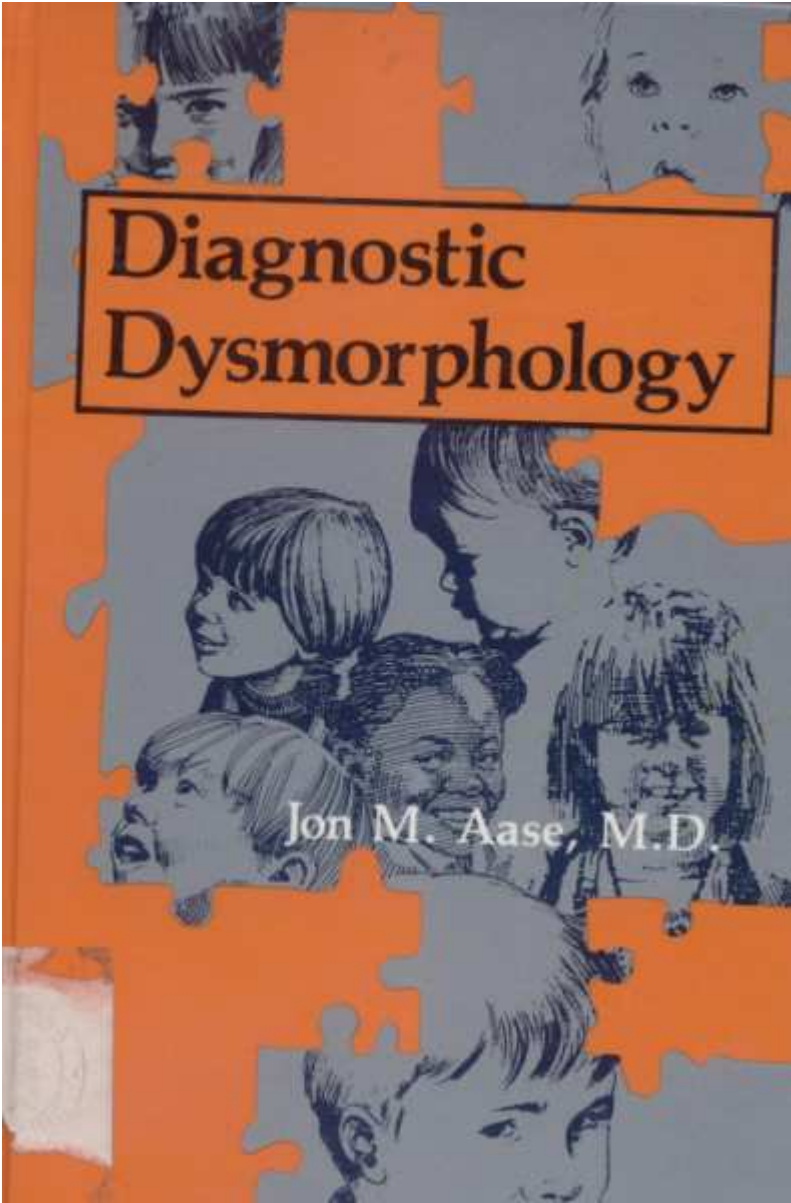
1.2. BIRTH DEFECTS

About 3% of all the children born in any hospital or in any country or in any year will have a significant congenital abnormality—one which is of more than cosmetic concern and which, uncorrected, will interfere with normal functioning (Fig. 1.1A). Although such anomalies occur in only a small fraction of all newborns, they cause a much larger proportion of neonatal and infant deaths, and children with birth defects make up about 30% of all admissions to pediatric hospitals. Furthermore, these problems appear, by definition, at the very start of life, and many affected individuals require chronic care for decades. The burdens imposed on these people, their families, and society at large are enormous. As yet, the great majority of birth defects are neither detectable by prenatal diagnosis nor preventable, and thus the impact of these problems has not decreased despite all the advances in other areas of pediatric medicine.

Almost all birth defect syndromes are exceedingly rare, and a practicing physician would be expected to see only a handful of such cases in his or her professional lifetime, yet there are so many different disorders that even a specialist in the field will never gain experience with all of them. Therefore, the approach set forth here depends not on rote memorization of the features of rare syndromes but on recognition and analysis of their component anomalies.

For purposes of conceptualization as well as for ease of discussion, it is helpful to divide birth defects into those affecting one or several organ systems (Fig. 1.1B). A further

J. M. Aase "Diagnostic Dysmorphology"
Plenum Medical Book Company, 1990



Diagnostic Dysmorphology

Jon M. Aase, M.D.

Tabella 1 Anomalie congenite: classificazione e stima dell'incidenza e dell'esito annui delle gravidanze in Europa (nascite annue totali $\cong 13.6 \times 10^6$)

Categoria anomalia	Numero per 1000 nati vivi	Nascite per anno	Esito delle gravidanze						Principali necessità terapeutiche
			Mortalità neonatale		Inabilità permanente		Trattamento efficace		
			No.	%	No.	%	No.	%	
• <u>Malformazioni congenite</u>	30.0	<u>408 300</u>	89 800	22	98 000	24	220 500	54	<u>Chirurgia pediatrica</u> <u>Sostegno sociale</u> <u>Trattamento medico e sostegno</u>
• <u>Anomalie cromosomiche</u>	3.2	<u>43 700</u>	14 800	34	28 000	64	900	2	
• <u>Malattie ereditarie</u>	7.0	<u>95 200</u>	55 200	58	29 500	31	10 500	11	
Totale	40.2	<u>547 200</u>	159 800	<u>29</u>	155 500	<u>28</u>	231 900	<u>43</u>	

Da: WHO Advisory Group on Hereditary Diseases (1) e Czeizel & Sankaranarayanan (2)

Da: WHO Advisory Group on Hereditary Diseases (1) e Czeizel & Sankaranarayanan (7).
1985

Oltre mezzo milione di bambini su ~ 13 milioni (~4%) nati in 1 anno presentano una grave anomalia congenita

Tabella 14.3 – Cause di difetti congeniti

Eziologia	Prevalenza %
<i>Genetica</i>	30-40
Cromosomica	6
Mendeliana	7,5
<u>Multifattoriale</u>	<u>20-30</u>
<i>Ambientale</i>	5-10
Farmaci e agenti chimici	2
Infezioni	2
Malattie materne	2
Agenti fisici	1
<u>Cause non note</u>	<u>50</u>

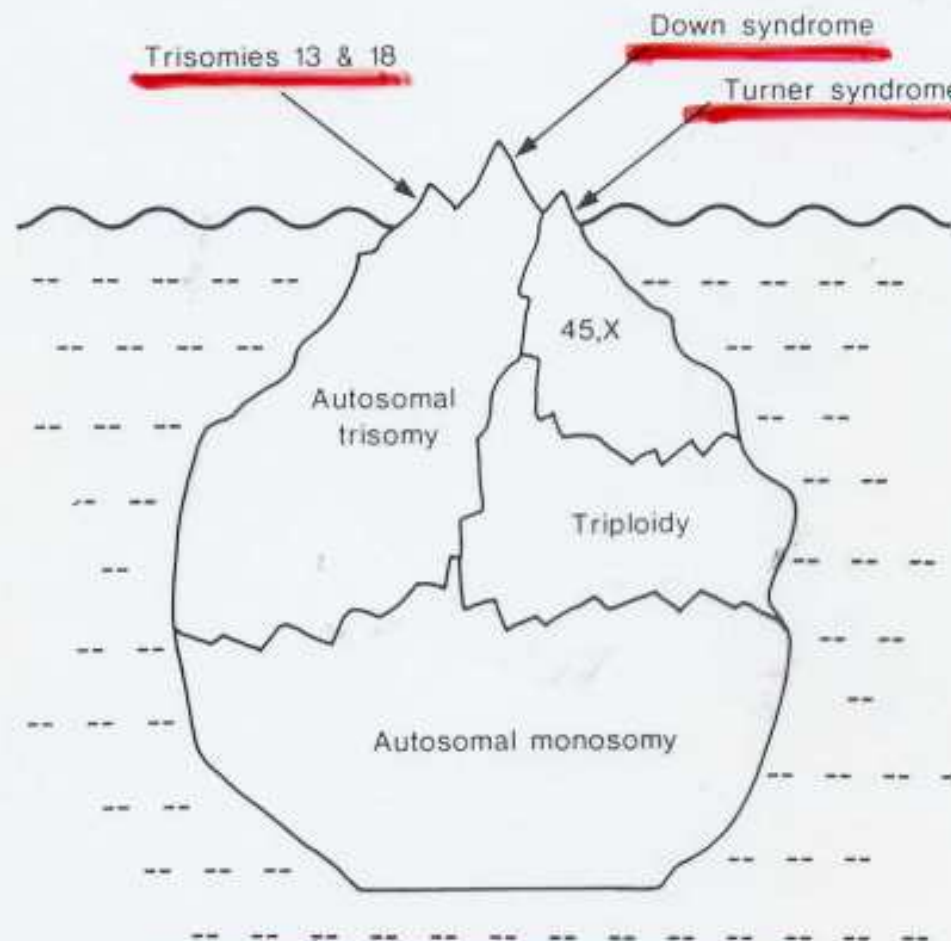
REPRODUCTIVE FAILURE

FIGURE 20-1. The iceberg of chromosomal pregnancy loss.

Although far less dramatic than legionnaire's disease, toxic shock syndrome, or AIDS, severe congenital birth abnormalities are far more common, affecting two to four infants in every 100 births. Thus, in aggregate and over many years, birth anomalies have a great impact on our economy. And surely they generate considerable emotional erosion. Yet apart from the National Foundation March of Dimes, there have been few large organizations that have supported investigation of birth anomalies, and none has been concerned with the training of dysmorphologists.

The dysmorphologist or syndromatologist is often thought of by other clinicians as being lost in arcane details, obsessed with minutiae, speaking in tongues beyond the realm of professional comprehension, understood by none except those similarly engaged. On the other hand, the consulting family perceives the dysmorphologist as one who knows all, who will provide a diagnosis and answer all questions about prognosis and therapy. In truth, neither of these views is correct.

There is probably no other area of endeavor in which failure to diagnose is accepted as the norm. Could one practice surgery or civil engineering or law and fail so often, yet be considered an expert? Under no circumstances! Nevertheless, it has been demonstrated repeatedly that the best of us has no greater than a 20% overall rate of success. Surely it must be the only field in which one can perform so dismally yet be considered competent.

There is something metaphysical about naming a disorder. All concerned—the patient, the clinician, the parents—seem to experience a certain satisfaction or sense of security when an unknown condition is defined. This is valid, since understanding has its incipience in definition. The unknown is scary. Once the condition has been measured and its extent limned, its recognition is made easier. Thereby, interest and concentration can be more easily focused upon it. This, in turn, may lead to therapy and control.

Reaching a diagnosis in a child with congenital abnormalities bears many similarities to the work of a detective in solving a crime. The physician is confronted with the end product of events that took place weeks or months before, unseen and usually unsuspected. He must use every available physical clue, together with the testimony of "witnesses," to try to reconstruct the crime. If he can solve the mystery and identify the cause of the malformation, he can provide invaluable help for the victim and his family. In some rare instances, the "culprit" can be permanently removed from circulation, as in the case of thalidomide and, it is to be hoped, rubella.

Surely the fictional archetype for observation and deduction is Sherlock Holmes. His uncanny ability to construct logical chains of reasoning from the most obscure evidence has made his name synonymous with the word "detective." I heartily recommend the stories of Arthur Conan Doyle as bedtime reading for anyone interested in the art and science of observation. A number of quotations from these works have been inserted at appropriate places in this text, not so much as "comic relief," as to emphasize the value of certain general principles in the diagnosis of dysmorphic conditions.

While the detective analogy should not be stretched too far, the principles of careful data gathering, minute observation of subtle physical clues, and deductive reasoning do form the basis of dysmorphologic diagnosis, and these techniques are incompletely addressed in textbooks of physical examination and compilations of birth defect "syndromes." This book is intended to describe the methods used by dysmorphologists to gather clues from the history and physical examination and to outline the reasoning processes used to reach a meaningful diagnosis. It is intended primarily for the instruction of house officers, fellows, and practicing physicians, and assumes a background in clinical medicine and, particularly, pediatrics.

Jon M. Aase

Albuquerque, New Mexico

1.1. EMBRYOLOGY

1.1.1. Developmental Timing

Prenatal development may be conveniently divided into three time periods: the implantation stage, extending from the time of fertilization of the egg to the end of the third week of gestation, the embryonic stage, from the beginning of week 4 to the end of week 7, and the fetal stage, from week 8 until birth.

During the implantation stage, rapid cell proliferation leads to the formation of the hollow blastocyst, within which develops the embryonic plate. The amniotic cavity appears, and primitive circulatory connections with the placenta are established. Early cell differentiation begins late in this period, with somites demarcated in the mesodermal layer, and longitudinal folds of neuroectoderm indicating the site of the future brain and spinal cord.

The embryonic stage is the time of primary tissue differentiation and the formation of definitive organs. Neural tissues undergo very rapid proliferation, with closure of the neural tube and flexion of its anterior segments to form the divisions of the developing brain. The heart begins to beat, allowing blood to circulate through the newly formed

Errori della morfogenesi

□ —————→
Sviluppo normale

△ - - - - - →
malformazione difetto intrinseco
morfogenesi di un organo (es: cardiopatie,
NTD) (entro 8^a s.g.: fine organogenesi)

□ ————▼———→
distrusione danno di un tessuto/organo
già formato da causa estrinseca (es: bande
amniotiche → amputazione arti)

□ —————→
Deformazione ^(forma, posizione) sviluppo abnorme di una struttura
causato da forze estrinseche o intrinseche meccaniche
(es: compressione intrauterina, lesioni SNC con ↓ mobilità)
(dopo 8^a s.g.)
es: pie di torti
lussazione anca

TABLE 9.5 Classification of birth defects

Defect	Examples	Causes and genetic implications
• <u>Malformation</u>	Cleft lip/palate Cardiac defects Neural tube defects	Most isolated malformations show <u>multifactorial inheritance</u>
• <u>Disruption</u>	Cataracts caused by congenital rubella Limb defects caused by amniotic bands	Caused by <u>environmental factors</u> . Recurrence risk is usually very low
• <u>Deformation</u>	Congenital hip dislocation Talipes (club foot)	Caused by <u>mechanical compression</u> . Recurrence risk depends on cause
• <u>Dysplasia</u>	Skeletal dysplasias, e.g. achondroplasia	Often caused by <u>single-gene defects</u>
• <u>Sequence</u>	Potter (oligohydramnios) sequence	Usually sporadic with low recurrence risk
• <u>Syndrome</u>	Apert syndrome, Down syndrome, fetal alcohol syndrome	Can be <u>chromosomal, single gene or non-genetic</u>
• <u>Association</u>	VATER association (<u>v</u> ertebral, <u>a</u> nal, <u>t</u> racheo- <u>e</u> sophageal and <u>r</u> enal abnormalities)	Not genetic, although <u>cause is not known</u>

Difetti congeniti (Birth defects)

("Malformazioni" congenite)

.Maggiori {
• intervento chirurgico
(DTN, cardiopatie, LPS, agenesie renale)
• interferenza con la funzione

.Minori
(lievi) {
• no conseguenze mediche rilevanti
• no interferenze funzionali
(capelli soprannumerari, clinodattilie 5° dito)

.Incidenza:

- Difetti maggiori alla nascita 2-3%
- " " entro 3-5 anni 2% } 5%
- Difetti minori 10%

Totale 15%

.mortalità infantile (25% entro 1 anno)

.Nel 50% dei casi: cause ignote

(anomalie vascolari? mutazioni mendeliane?)

NB: basso rischio di ricorrenza
a/simmetrie delle lesioni

.D.c. isolato? cercarne altri...

Parametri di crescita

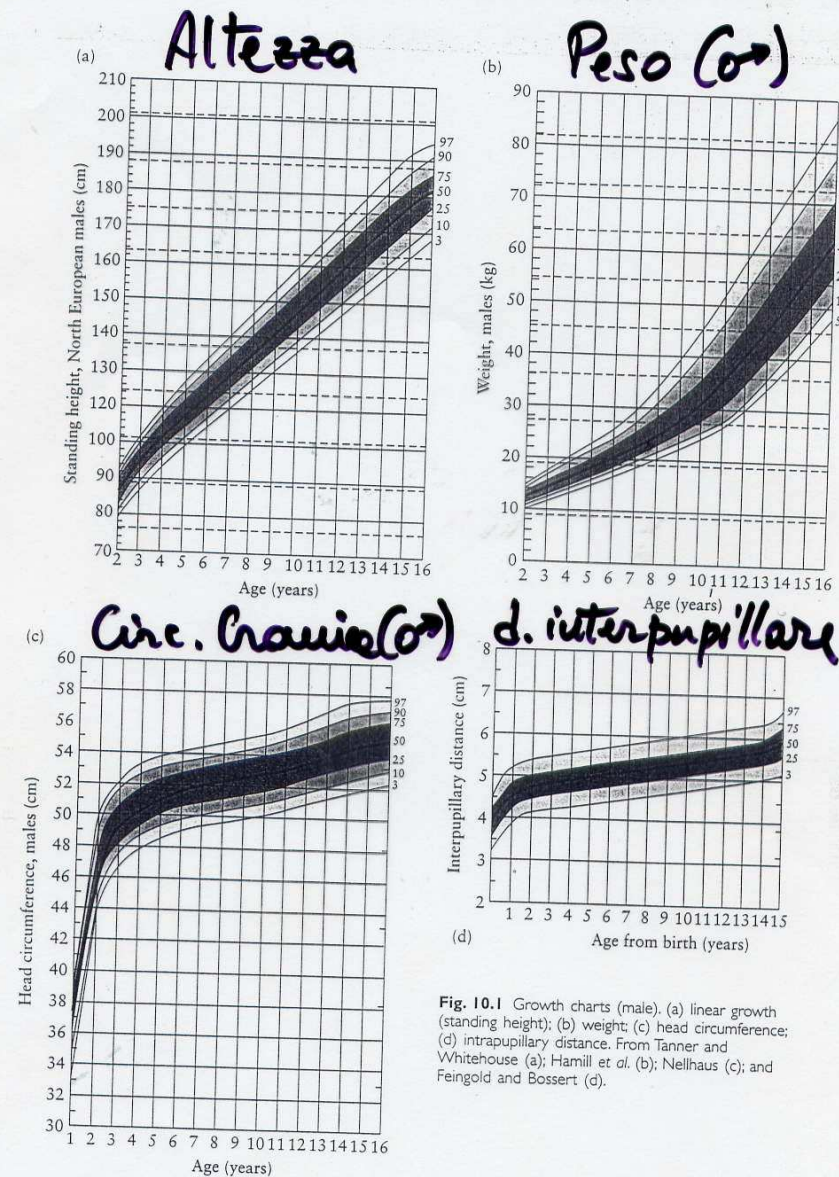


Fig. 10.1 Growth charts (male). (a) linear growth (standing height); (b) weight; (c) head circumference; (d) intrapupillary distance. From Tanner and Whitehouse (a); Hamill et al. (b); Nelhaus (c); and Feingold and Bossert (d).

Deformation (Secondary effect)

- Compression or biomechanical distortion of an already normally formed body part which usually occurs after 8 – 10 fetal weeks

Ex: club feet, plagiocephaly, torticollis, contractures, dimples, joint dislocations



Figura 14.10 – Deforma-
zione: piedi torti congeniti

Disruption (Secondary defect)

- **Compression / biomechanical distortion of an already formed (or to be formed) normal body part to such an extreme that the resulting defect looks like an anomaly**

Ex: oligodactyly due to amniotic bands,
cleft palate due to glossoptosis;
web neck due to nuchal edema



Major Anomaly

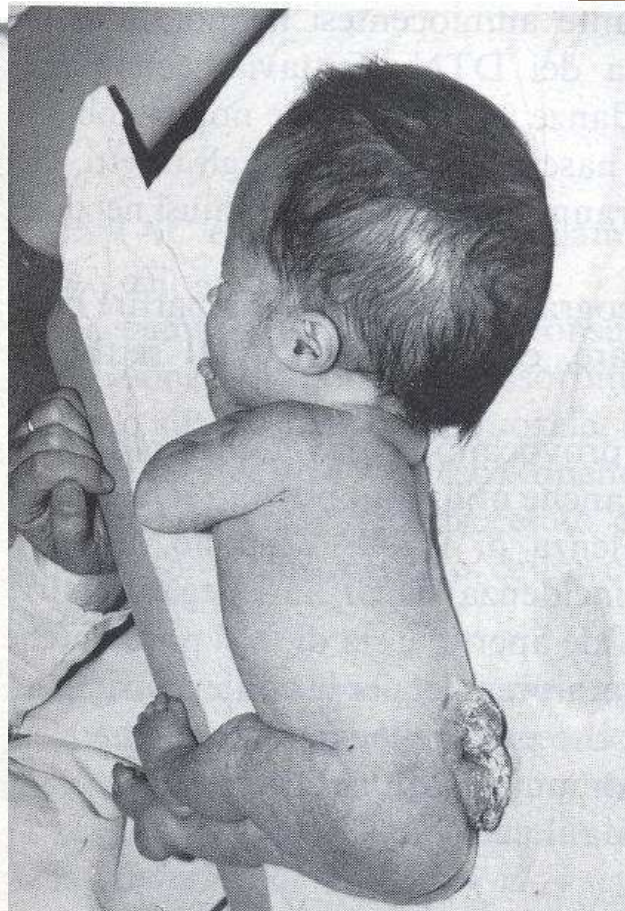
- **Basic alteration in embryological development severe enough to require intervention and which potentially has a long-term impact medically and/or psychologically**

Ex: spina bifida, omphalocele, bilateral cleft lip/palate, anophthalmia

Anomaly (Primary Defect)

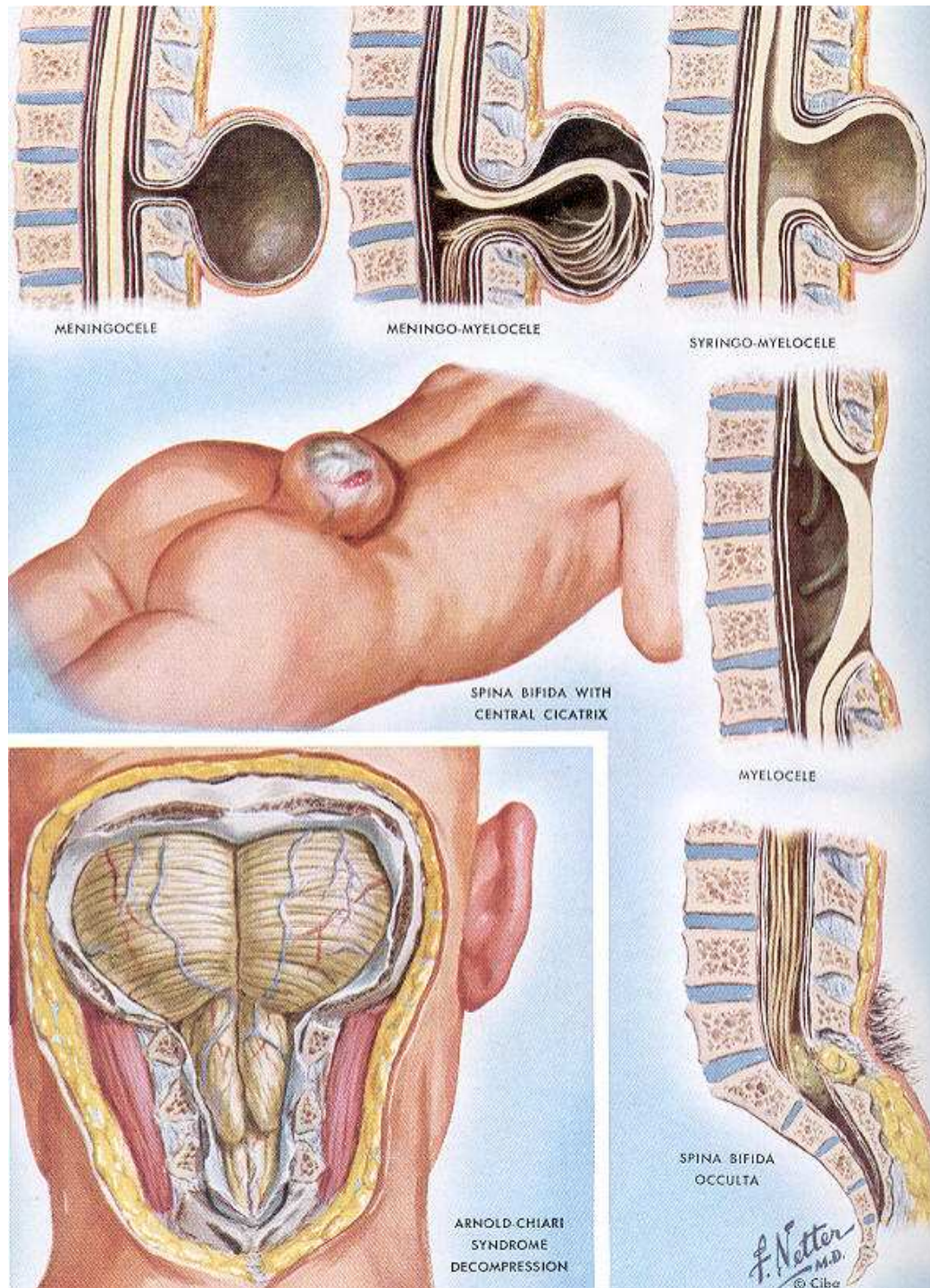
- Basic alteration in structure of a body part usually occurring by 8 – 10 fetal weeks

Examples: cleft lip, phocomelia, anencephaly



NTD
Neural
Tube
Defects

NB: Folate!!!



NDT Encefalocele



NDT Anencefalia





LS - LPS

Labioschisi (labbro leporino)
Labiopالاتو schisi



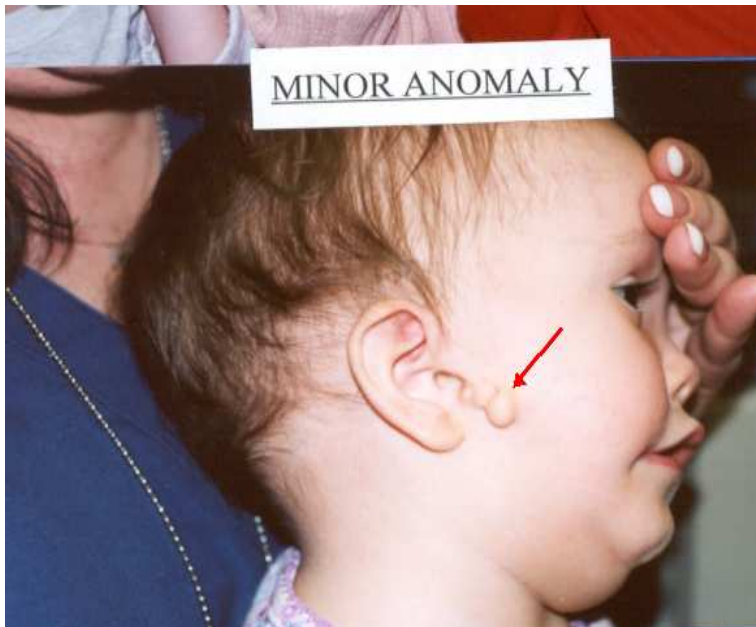
Figura 14.7 - Malformazioni. A) labioschisi monolaterale; B) labioschisi bilaterale; C) labiopالاتo schisi

Minor Anomaly

- Basic alteration in embryological and/or fetal development which requires no treatment or can be, more or less, corrected

Ex: postaxial polydactyly, absent digital flexion creases, low-set ears, preauricular tag

Minor anomalies





Polidattilia

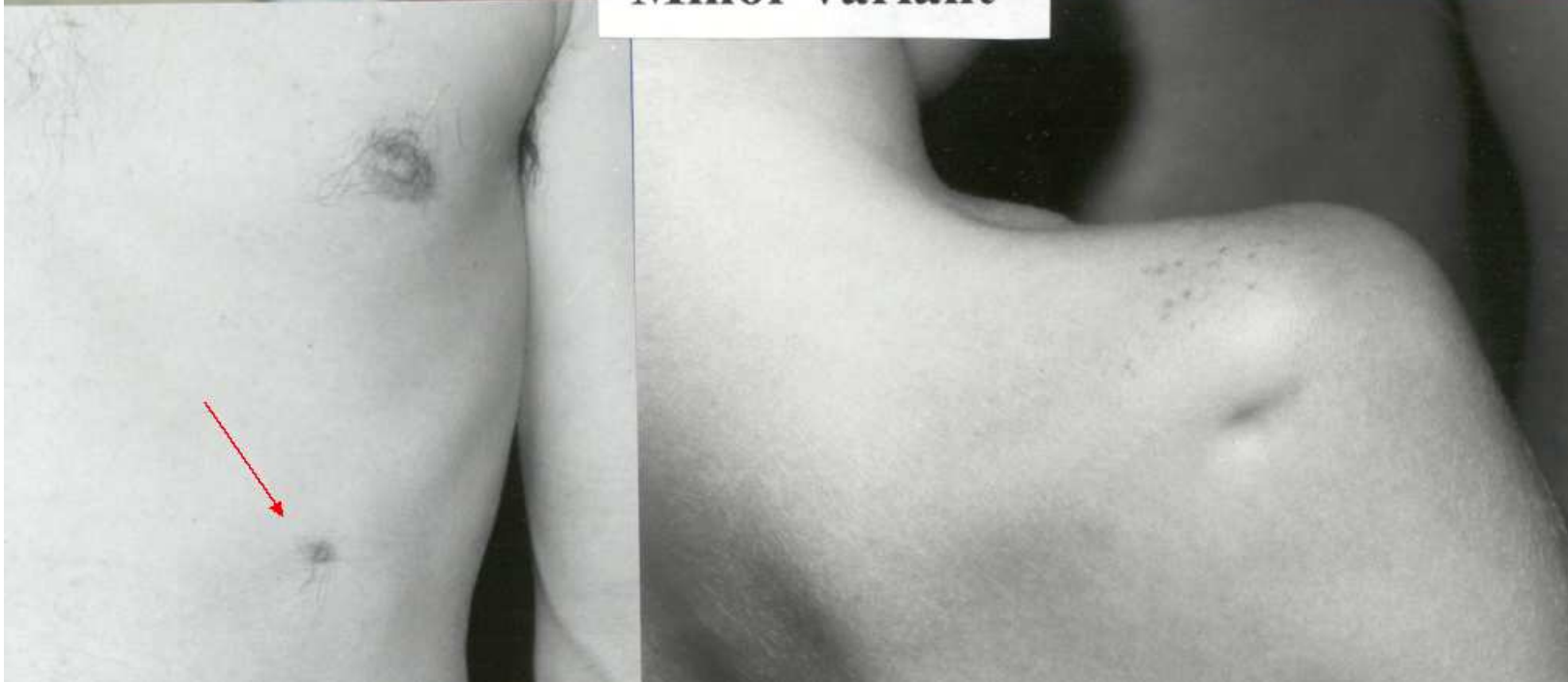
Minor / Normal Variant Feature

- Low frequency (1% - 5%) congenital feature found in the normal population or as an integral part of a multiple congenital anomaly syndrome

Ex: simian line, 5th finger clinodactyly, 2-3 toe syndactyly, epicanthal fold, accessory nipple



Minor variant



Multiple Congenital Anomalies (MCA)

- Two or more structural primary defects in two or more body areas, or in embryologically different areas
- Usually associated with a potentially recognizable syndrome

Syndrome

- Recurring pattern of structural defects and/or secondary effects/defects that allow for secure recognition
- Combination of features most likely represents a specific etiology



Sequence

- A situation where a single event (usually undefined) leads to a single anomaly (or situation) which has a cascading effect of local and/or distant deformations and/or disruptions

Potter sequence

Agenesia renale (bilaterale)



Oligoidramnios



Compressione fetale (faccia, arti)



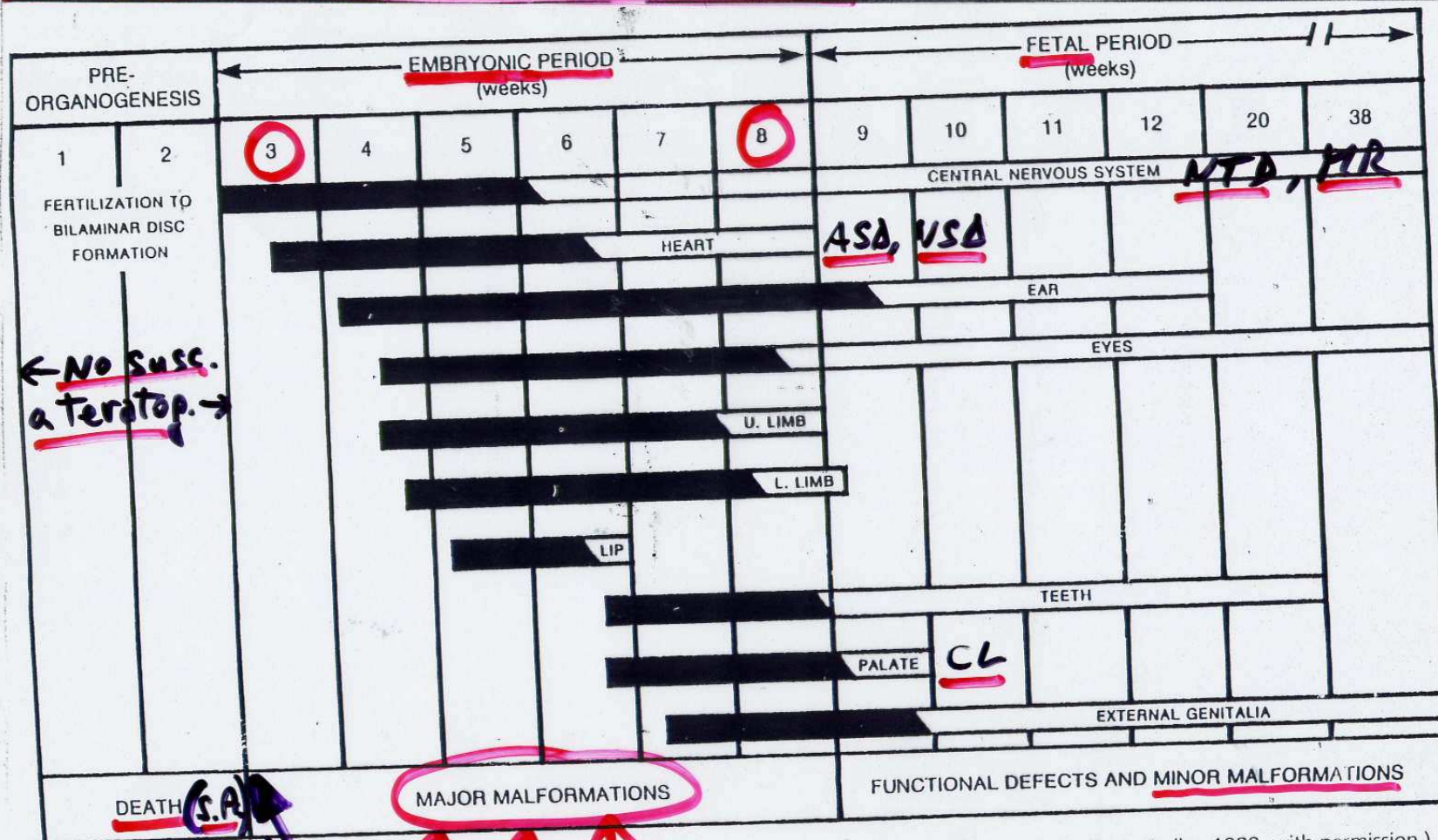
Ipoplasia polmonare



Morte x insuff. respiratoria



Susceptibilità ai TERATOGENI



← No Susc. a teratop. →

(Pre-implant.)

GASTRULATION

Black bars indicate highly sensitive periods. (From Sadler, 1989, with permission)

Tabella 14.7 – Esempi di agenti fisici a rischio per il feto

Agente – Effetto

- radiazioni ionizzanti, dosi elevate – microcefalia, difetti oculari, nuove mutazioni, tumori
 - calore/ipertensione elevata e protratta – difetti del tubo neurale, altri difetti del SNC, ritardo mentale
 - oligoidramnios/gravidanze gemellari/ malformazioni uterine – deformità da posizione, difetti in riduzione degli arti, ipoplasia mandibolare
 - bande amniotiche – sindattilia, amputazioni degli arti, schisi facciali atipiche, encefalocele, toracogastroschisi, difetti oculari
-

Tabella 14.8 - Esempi di patologie metaboliche e genetiche materne, a rischio per il feto

Fattore di rischio – Effetto

- *Diabete mellito insulino-dipendente* – cardiopatie, difetti del tubo neurale, renali, schisi facciali, oloprosencefalia, sindrome da regressione caudale
 - Distrofia miotonica* – distrofia miotonica ad esordio connatale, artrogriposi, cardiopatie, cataratta, ritardo mentale
 - *Fenilchetonuria* – ritardo mentale, ritardo di crescita, microcefalia
-

Natimortalità

. Cause (genetiche)

Cromosomiche 5-10%

M. mendeliane (es. nanismo

letali: OI, DT, acondrogenesi)

→ Cariotipo neonato (sangue
o fibroblasti)

→ Fotografie e Rx!

→ Esame autopsico

→ Conservazione campioni
biologici (di retrospettive)

Tabella 2.9. Prevenzione primaria e secondaria dei difetti congeniti

Prevenzione primaria (fase pre-concezionale)

- Individuare e correggere affezioni materne potenzialmente responsabili di difetti congeniti: diabete, endocrinopatie, epatopatie, ecc.
- Sierologia complesso TORCH. Vaccinazione soggetti non immuni (rosolia) e consigli circa le misure igieniche atte a prevenire altre infezioni
- Informare circa gli effetti teratogeni di alcuni farmaci
- Dissuadere da stili di vita non idonei in gravidanza (fumo, alcool, droghe, ecc.)
- Consigliare l'assunzione di acido folico in epoca pre-concezionale e nella fase organogenetica

Prevenzione secondaria (fase post-concezionale)

- Osservanza scrupolosa delle norme dell'igiene della gravidanza, con particolare attenzione all'alimentazione
- Realizzazione di programmi di screening ecografici e biochimici dei difetti congeniti nella popolazione non a rischio
- Diagnosi prenatale invasiva dei difetti congeniti
- Monitoraggio accurato delle gravidanze a rischio

FOURTH
EDITION

Smith's
Recognizable
Patterns of
Human Malformation

JONES

Prenatal Testing in a Fetus at Risk for Autosomal Dominant Polycystic Kidney Disease and Autosomal Recessive Junctional Epidermolysis Bullosa With Pyloric Atresia

Alberto E. Turco, Bernard Peissel, Sandro Rossetti, Angelo Selicorni, Siranoush Manoukian, Alberto Brusasco, Gianluca Tadini, Andrea Galimberti, Beatrice Tassis, Licia Turolla, Romano Tenconi, and Pier Franco Pignatti

Institute of Biological Sciences and Genetics, The University of Verona School of Medicine, Verona (A.E.T., B.P., S.R., P.F.P.); Cytogenetic Laboratory, ICP, Clinica Mangiagalli (A.S., S.M.), Center for Inherited Cutaneous Diseases, I Department of Dermatology and Pediatric Dermatology, University of Milan (A.B., G.T.), I Department of Obstetrics and Gynecology, University of Milan, Milan (A.G., B.T.); Department of Pediatrics, Section of Medical Genetics, University of Padua, Padua (L.T., R.T.), Italy

Amniocentesis and fetal skin biopsies were performed at 18 weeks of gestation in a fetus at risk for autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive junctional epidermolysis bullosa (EBJ) with pyloric atresia. A previous son of the couple under investigation had died at 3 months of EBJ. The mother of the propositus has ADPKD. Genetic linkage studies were carried out in 11 relatives (4 with ADPKD), and on fetal DNA obtained from cultured amniocytes, using 8 flanking DNA markers tightly linked to the PKD1 locus on chromosome 16p, and a DNA marker linked to another putative ADPKD locus on chromosome 2p. The linkage results indicated that the fetus had not inherited the ADPKD chromosome from the affected mother, with a diagnostic accuracy of >99%. Ultrastructural and immunohistochemical analyses of multiple fetal skin biopsies showed no EBJ-associated abnormalities. Thus, combining recent morphological and molecular diagnostic methods, we could show that the fetus was free from both diseases. After 40 weeks of gestation, a normal male infant was delivered.

